amorphous forms are high-energy, low-density solids that can yield transient dissolution rates considerably greater than crystalline solids.

Liquid crystals are an intermediate state in which the molecules in a crystal can undergo a secondary phase transition to a mesophase, which gives them mobility in 1–2 directions. They are birefringent, but possess flow properties like a liquid phase. Lyotropic liquid crystals form on uptake of water into a system that increases its mobility, and thermotropic liquid crystals can be disrupted by heating above a transition temperature. Cromolyn sodium (Cox et al., 1971), the HMG-CoA reductase inhibitor SQ33600 (Brittain et al., 1995), and the leukotriene D4 antagonist L-660,711 (Vadas et al., 1991) are examples of pharmaceuticals that can form liquid crystals.

The crystal *habit* or external shape may differ when drugs are recrystallized from different solvent systems without changing the internal structure. The presence of additives, the rate of cooling, degree of agitation, and the degree of saturation can all affect crystal habit (Byrn, 1982; Byrn et al., 1999). Habit can affect bulk properties such as density and flowability (Carstensen, 1993) or influence the ability to filter crystals during purification. Chow and Grant (1988) have shown that the dissolution rate of acetaminophen can be altered two to three times by modifying the length to width ratio through incorporation of additives. In general, habit effects on solubility are transient and of a magnitude equivalent to particle-size reduction techniques.

In summary, most drugs are developed as crystalline forms, which have the greatest physical and chemical stability, so that their purity can be increased during recrystallization. Knowledge of the potential polymorphic forms may allow the development scientist to find a metastable form with the prerequisite stability and increased dissolution rate to make it the desirable marketed form. Anhydrate forms usually give faster dissolution rates and higher aqueous solubilities than the hydrated form. Other solvates are not commonly used in pharmaceutical systems owing to potential toxicity of the solvent, but may provide additional solubility enhancement. Amorphous forms have the highest free energy, with the greatest degree of solubility enhancement, but are the most difficult to stabilize against transformation to the stable crystal form. The remainder of the chapter describes the advantages and disadvantages of each type of solid and gives numerous examples from the pharmaceutical literature where alteration of the solid form resulted in increased solubility.

Methods to Study the Solid State during Preformulation Screening

After initial selection of the candidate drug and its salt form (if applicable), it is recommended that a purposeful effort be undertaken to examine the solid states available for development consideration. Balbach and Korn (2004) have offered suggestions on how to screen candidates with small quantities of material. In the absence of such programs, new crystalline forms may be discovered by accident from precipitation of less soluble phases or a change in appearance of the bulk drug during scale-up. If sufficient formulation, analytical, and toxicology work has been completed and it becomes necessary to change the solid state, it may significantly delay the development program. If the newly discovered form is the more stable modification, it may be difficult to reproduce the metastable form. Carstensen (1993) noted that the diazepam tablet development program was complicated by the crystallization of a more stable polymorph after clinical trials had begun. A classic example of an unexpected occurrence of an earlier unidentified polymorph is that of Ritonavir. Bauer et al. (2001) have described how Norvir capsules had unknowingly been manufactured at a level that was supersaturated relative to the most stable conformational polymorph. It was not until several lots of the product failed dissolution testing that the new polymorph was identified.

Byrn et al. (1995) have offered strategic approaches for characterizing pharmaceutical solids with specific emphasis on regulatory considerations. The International Conference on Harmonisation (2000) and the FDA (2004) have also presented their guidance for industry on how to address